Original Article

Biologics in Chronic Rhinosinusitis: An Update and Thoughts for Future Directions

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Abstract

Background: Potential biologic therapies for chronic rhinosinusitis (CRS) is a growing field of interest and research. Biologics target specific immune cells or inflammatory pathways within a disease process, increasing drug efficacy while reducing complications. The success of biologics in other inflammatory conditions such as asthma and atopic dermatitis has spurred much of the corresponding research in CRS. A rapid expansion in the volume of research concerning biologic therapies with potential crossover to treating CRS has made it difficult to stay current. Furthermore, much of the literature has been focused on allergy, asthma, and immunology subspecialties. As the role for biologic therapies in CRS continues to expand, it is increasingly important for otolaryngologists to remain up to date on their progression.

Objective: The objectives of this review are to provide an update on the growing field of biologics for otolaryngologists who treat CRS and discuss potential future areas of research.

Methods: A literature review of biologic therapies studied in CRS was performed. In addition, a detailed review of all biologic therapies targeting inflammatory markers involved in Th1-, Th2-, and Th17-mediated inflammation was performed to identify potential areas for future research. The role for biologic therapies in CRS, endotypes of CRS, current biologic therapies studies in CRS, and future areas for research were reviewed.

Results: Sixty-nine unique biologic therapies have been developed for Th1-, Th2-, and Th17-mediated inflammation. Five biologics are currently being investigated for use in patients with CRS with nasal polyposis.

Conclusions: As the field of biologics continues to expand, remaining up to date on the current literature may help clinicians identify patients who may benefit from biologic therapies. In addition, ongoing research in other inflammatory disorders with shared pathophysiology to CRS may reveal other potential therapies for CRS that have not previously been investigated.

Keywords

biologic therapy, Th17, biologics, inflammation, chronic rhinosinusitis, systemic therapy, Th2, polyps, Th1, eosinophilia

Introduction

Chronic rhinosinusitis (CRS) is a common inflammatory condition affecting the paranasal sinuses.[1] According to current consensus guidelines, patients with CRS are initially treated with appropriate medical therapy, and patients with persistent symptoms may elect to pursue endoscopic sinus surgery (ESS).[1,2] However, not all patients with CRS are alike. Some patients respond to medical management alone, others benefit from a combination of surgical and medical therapy, and others fail to gain control of their symptoms despite varied combinations of medications and revision surgeries.[3] Physicians treating CRS currently have limited therapeutic options to treat one of the most prevalent, costly and crippling chronic inflammatory diseases.[1,3–5] However, as the pathophysiology underlying this disease process has been better defined, the potential for

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personalized targeted therapy to treat CRS is beginning to emerge.[6,7]

Biologic therapeutics target specific immune cells or inflammatory pathways within a disease process, theoretically increasing drug efficacy and reducing complication rates compared to traditional therapies.[8] Several biologic therapies have been developed and approved for use in patients with severe recalcitrant asthma, as well as atopic disease, with clinical trial data showing tremendous efficacy in controlling the associated underling inflammation.[9,10] Atopy and asthma are common comorbidities in CRS, and asthma has significant overlapping pathophysiology with CRS with nasal polyposis (CRSwNP).[1,10] As biologic therapies were undergoing early investigation for asthma, patients with concurrent CRSwNP were noted to experience incidental improvements in their sinonasal symptoms.[11] Subsequent clinical trials focused on the effects of biologics on CRSwNP demonstrated groundbreaking improvements in polyp burden.[12,13] This effort led to a rapid expansion in the volume of research concerning biologic therapies and their potential role in treating patients with CRS, with research findings outpacing peer-review publications, making it difficult to stay current in the field. Furthermore, much of the available literature can only be found in the allergy, asthma, and immunology literature. The objectives of this review are to provide an update on the growing field of biologics for otolaryngologists who treat CRS and discuss potential future areas of growth in our specialty.

The Role of Biologic Therapies for CRS

Patient Selection

Biologic therapies are currently being investigated for patients with recalcitrant disease with nasal polyps. While the majority of patients receive significant benefit from appropriate ESS, a proportion of patients will continue to suffer despite continued postoperative medical therapy.[9,14,15] These patients typically have more severe phenotypes of CRS, such as aspirin-exacerbated respiratory disease, severe combined upper airway disease, immunodeficiencies, and/or systemic inflammatory diseases.[16] Ultimately, the inflammation in these patients is challenging to control and often requires multiple or continuous courses of oral corticosteroids, revision surgeries, or less utilized medical therapies such as topical antibiotics or surfactants.[3] Given the limited evidence available, as well as the lack of clear guidelines and indications, these recalcitrant patients are the current targets for biologic therapies. The majority of research and development is currently focused on CRSwNP, although clinical trials on the effects of biologics in eosinophilic CRS are also underway.[6,8,17]

Benefits of Biologic Therapies

Corticosteroids have become the cornerstone of medical therapy for CRS. While topical intranasal corticosteroids are considered safe for long-term use, systemic corticosteroids are associated with significantly more risk.[1] Long-term or high-dose systemic corticosteroid use is associated with multiple complications including adverse changes in bone mineral density, adrenal suppression, avascular necrosis, cataracts, and psychosis.[18] The dose required to put patients at increased risk remains unclear, but in general, multiple courses of systemic corticosteroids should be used cautiously in patients with CRS.[18] In addition to the potential of biologic therapies to control inflammation in recalcitrant patients, they could also potentially reduce systemic corticosteroid use.[19] Biologics are a particularly attractive avenue for patients who require multiple doses of systemic corticosteroids for disease control or become dependent on systemic corticosteroid. Having less systemic effects, these targeted therapies are aimed to decrease the inflammation that corticosteroids are prescribed to treat, potentially decreasing the use and subsequent risks of systemic corticosteroid use. The risks of biologic therapies will be discussed separately later, after the individual therapies have been introduced.

Endotypes of CRS

Historically, CRS has been divided into 2 distinct phenotypes: (1) CRSwNP and (2) CRS without nasal polyps (CRSsNP).[1] It is becoming clear that this is a gross oversimplification of a broad and diverse disease. Growing evidence has emerged suggesting multiple endotypes exist within CRSsNP and CRSwNP.[20] In the context of biologic therapies, it is appropriate to discuss CRS endotypes based on their inflammatory pathophysiology, whereby 3 main inflammatory pathways have been identified: Th1, Th2, and Th17 (Figure 1).[16] Th1-driven inflammation is generally associated with CRSsNP and predominately characterized by increased neutrophils, which is associated with myeloperoxidase, and elevated levels of interferon (IFN)-γ, interleukin (IL)-2, and tumor necrosis factor (TNF)-α.[6,16] Th2-mediated inflammation is associated with Caucasian patients with CRSwNP and primarily characterized by increased eosinophils and elevated levels of IL-4, IL-5, IL-10, IL-13, and eosinophil cationic protein.[6,16,20] Immunoglobulin E (IgE), which is associated with allergic hypersensitivity, is also typically elevated in patients with CRSwNP.[6,20] The Th17 pathway was recently described to be dominant in Asian patients with CRSwNP and is associated with increased expression of IL-6, IL-17, IL-22, and TNF-α.[21,22] Recent research has suggested that these pathways may be dominant or mixed in patients with

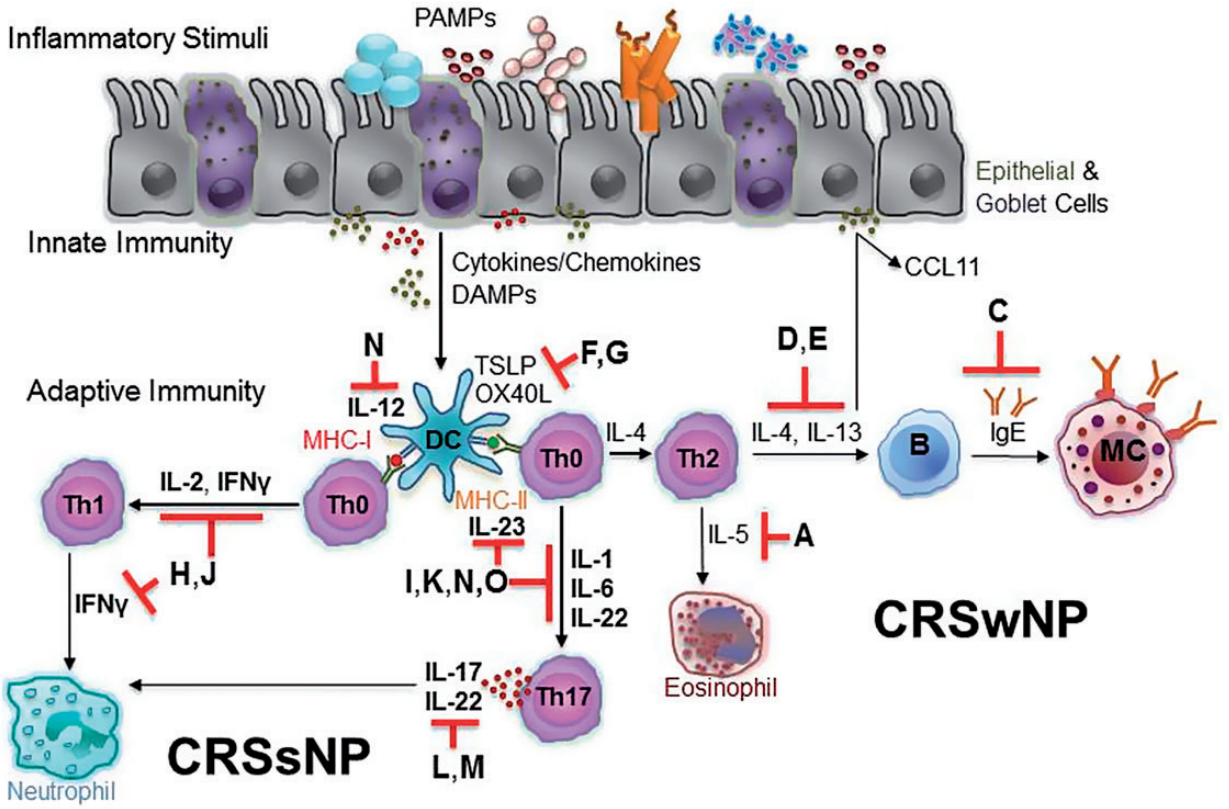

Figure 1. Schematic illustrating the pathophysiology of CRS with respect to subtype (CRSsNP and CRSwNP) and endotype (Th1, Th2, and Th17) with corresponding innate and adaptive immune modulator targets for biologic therapies. The bolded letters indicate biologic therapies that have been approved for other inflammatory conditions with overlapping pathophysiology or are in clinical development for CRS, as referenced in Tables 1 and 2. CCL, C-C motif chemokine ligand; CRSsNP, chronic rhinosinusitis without nasal polyposis; CRSwNP, chronic rhinosinusitis with nasal polyposis; B, B cell; DAMP, danger-associated molecular pattern; DC, dendritic cell; IFN, interferon; IgE, immunoglobulin E; IL, Interleukin; MC, mast cell; MHC-I, major histocompatibility complex class I; MHC-II, major histocompatibility complex class II; OX40L, OX40 ligand; PAMP, pathogen-associated molecular pattern; Th0, T helper cell type 0; Th1, T helper cell type 1; Th2, T helper cell type 2; Th17, T helper cell type 17; TSLP, thymic stromal lymphopoitein.

CRS, resulting in primarily eosinophilic or noneosinophilic inflammation.[20] This pathophysiology is important to consider in the context of the mechanism of action of biologic therapies. Given that a substantial amount of literature addresses the evolving definitions of endotypes and phenotypes in CRS, this review will focus on available biologic therapies and potential for future development.

Current Biologic Therapies for CRS

The biologics currently in clinical trials for CRS are focused on patients with CRSwNP due, in part, to its overlapping pathophysiology with that of asthma.[17] There are currently no biologic therapies under investigation for noneosinophilic CRS nor for Th1- and Th17-mediated inflammation in CRS. Five monoclonal antibodies targeting CRSwNP, 3 of which are in phase 3 and 1 of which is in phase 2 clinical trials for eosinophilic CRS, will be discussed with respect to their biological target.[12,13,23,24] Table 1 details the therapies currently under investigation for CRSwNP, while Tables 2 and 3 describe all biologic therapies under development for other Th2- and Th1-mediated inflammatory diseases, respectively. The majority of these drugs have not been examined in CRS patients; thus, information regarding clinical trials was limited to the 5 drugs that have been examined for use in CRSwNP. The goal of Tables 2 and 3 is to highlight the research in other fields that may spark future research related to CRS.

Anti-IL-5 Therapy

IL-5 is essential for eosinophil survival, growth, recruitment, and activation.[82] Three monoclonal antibodies have been developed which target IL-5. Reslizumab and mepolizumab are currently in phase 3 clinical

Table 1. Biologic Therapies Under Investigation for CRSwNP.[a]

Target	Drug	Sample Size		Treatment Duration	Outcomes	Side Effects[b]	References
		Treatment	Control				
IL-5[A]	Mepolizumab	20	10	4 Weeks	1. Reduction in polyp size	Headache (19%), injection site reaction (8%–15%), and hypersensitivity reactions (1%–4%)	Gevaert et al.[23]
	Reslizumab	16	8	4 Weeks	1. Reduction in polyp size	Transient increase in creatine phosphokinase (20%) and anaphylaxis (<1%)	Gevaert et al.[24]
IgE[C]	Omalizumab	16	8	16 Weeks	1. Reduction in polyp size 2. Improved CT scores	Injection site reaction (45%), headache (6%–12%), nasopharyngitis (9%), cardiovascular complication (PE, DVT, MI, unstable angina; <3%), and anaphylaxis (<1%)	Pinto et al.[12]
		7	7	24 Weeks	1. Improved CT scores		Gevaert et al.[13]
IL-4Rα[D]	Dupilumab	30	30	16 Weeks	1. Reduction in polyp size 2. Improvement in symptoms	Injection site reaction (10%), conjunctuvitis (10%), HSV (2%–4%), and hypersensitivity/serum sickness (<1%)	Bachert et al.[25]

Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyposis; CT, computed tomography; DVT, deep vein thrombosis; IgE, immunoglobulin E; IL, interleukin; MI, myocardial infection; PE, pulmonary embolism; Rα, receptor alpha subunit.
[a]Only randomized control trials.
[b]Most common and/or serious adverse events.

trials for treating CRSwNP.[17] Systemic delivery of these biologics has demonstrated a significant reduction in polyp size measured using nasal endoscopy with concurrent reduction in peripheral eosinophil counts.[23,24] Unfortunately, neither medication resulted in significant symptomatic improvement in phase II trials.[23,24] These studies were limited by small sample sizes, a short duration of patient follow-up, and the absence of disease-specific quality of life (QOL) measures such as the sinonasal outcome test-22 (SNOT-22). Such additions to the phase 3 study design may help gauge the utility of these medications for the management of CRSwNP.

Having a similar targeted strategy, benralizumab was developed for the treatment eosinophilic asthma and has completed phase 3 clinical trials.[26] Benralizumab is an antibody against the IL-5 receptor, and its treatment has exhibited improvement in asthma symptoms and lung function as well as reduction in annual asthma exacerbations.[83] A phase 2 clinical trial examining the effects of benralizumab in eosinophilic rhinitis began in 2016; results are pending.[43]

Anti-IL-4 Receptor α Therapy

IL-4 serves key roles in the immune response of fibroblasts and polyp formation in CRS.[3] Dupilumab was approved for atopic dermatitis and is a monoclonal antibody to the α subunit of the IL-4 receptor (IL-4Rα) that inhibits signaling of IL-4 and IL-13.[25] IL-4 and IL-13 have overlapping roles in the pathogenesis of inflammation, in part due to their shared receptor affinity for IL-4Rα.[84] A randomized control trial that examined the effects of dupilumab in CRSwNP patients versus placebo demonstrated significant improvements in polyp size, disease-specific QOL, as measured using the SNOT-22 score, and objective olfactory function.[25] This study was limited by sample size and short duration of patient follow-up. However, dupilumab is the only biologic under investigation for CRSwNP that has been shown to improve disease-specific QOL and is currently in phase 3 clinical trials, representing a promising potential biologic therapy for CRSwNP.[43]

Anti-IgE Therapy

IgE is produced by plasma cells in response to a variety of stimuli, including allergen exposure. The specific role of IgE in the pathophysiology of CRSwNP remains unclear; however, increased levels of IgE have been measured in patients with CRSwNP with atopy and increased eosinophils.[36,85] IgE is a potent inflammatory mediator responsible for mast cell activation, further exacerbating inflammatory signaling.[86] Omalizumab is an anti-IgE monoclonal antibody approved for use in moderate-to-severe uncontrolled allergic asthma and

Table 2. Biologic Therapies Targeting Th2-mediated Inflammation.

Target	Drug	Indication	References
IL-5[A]	Mepolizumab	Asthma[a]	Gevaert et al.[23]
		EGPA, COPD, CRSwNP, hypereosinophilic syndrome, atopic dermatitis[b]	
	Reslizumab	Asthma[a]	Gevaert et al.[24]
		CRSwNP, EGPA[b]	
IL-5Rα[A]	Benralizumab	Asthma, COPD, EGPA, hypereosinophilic syndrome, eosinophilic CRS[b]	Tian et al.[26]
IL-5Rβ[A]	TPI ASM8	Asthma[b]	Imaoka et al.[27]
CCL11[B]	Bertilimumab	Bullous pemphigoid, CD, UC, atopic dermatitis, nonalcoholic steatohepatitis, macular degeneration[b]	Rosenwasser et al.[28]; Gonzaloet al.[29]
		Allergic rhinitis, ovarian cancer[c]	
IgE[C]	Omalizumab	Asthma, urticaria[a]	Belliveau[30]
		CRSwNP, mastocytosis, nephritis[b]	
	Ligelizumab	Asthma, bullous pemphigoid, urticaria[b]	Arm et al.[31]
		Atopic dermatitis[c]	
	Quilizumab	Asthma, allergic rhinitis, urticaria[c]	Harris et al.[32]
IL-4[D]	Pascolizumab	Asthma[c]	Kau and Korenblat[33]
	Altrakincept	Asthma, allergy, GVHD[c]	Kau and Korenblat[33]
IL-4Rα[D]	Dupilumab	Atopic dermatitis[a]	Kau and Korenblat[33]
		CRSwNP, asthma, eosinophilic esophagitis[b]	
	AMG 317	Asthma[c]	Kau and Korenblat[33]
	Pitrakinra	Asthma, atopic dermatitis[c]	Kau and Korenblat[33]
IL-13[E]	Lebrikizumab	Asthma, atopic dermatitis, alopecia areata[b]	Kau and Korenblat[33]
		COPD, idiopathic pulmonary fibrosis, UC[c]	
	Tralokinumab	Asthma, UC[c]	Kau and Korenblat[33]
	Anrukinzumab	Asthma[c]	Kau and Korenblat[33]
	GSK679586	Idiopathic pulmonary fibrosis, systemic scleroderma[b]	Kau and Korenblat[33]
IL-4/IL-13[D,E]	SAR156597	Asthma, atopic dermatitis[b]	Kau and Korenblat[33]
TSLP[F]	Tezepeluma[b]	Asthma, Allergic rhinitis[c]	Gauvreau et al.[34]
OX40L[G]	Oxeluma[b]	Asthma[a]	Paller et al.[35]
		EGPA, COPD, CRSwNP, hypereosinophilic syndrome, atopic dermatitis[b]	

Abbreviations: CCL, C-C motif chemokine ligand; CD, Crohn's disease; COPD, chronic obstructive pulmonary disease; CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyposis; EGPA, eosinophilic granulomatosis with polyangiitis; GM-CSF, granulocyte-macrophage colony stimulating factor; GVHD, graft versus host disease; IgE, immunoglobulin E; IL, interleukin; OX40L, OX40 ligand; Rα, receptor alpha subunit; Rα1, receptor subunit alpha type 1; Rβ, receptor beta subunit; TSLP, thymic stromal lymphopoitein; UC, ulcerative colitis.

[a]Approved for use (see references for specific indications).

[b]Currently under investigation for clinical use for this indication.

[c]Discontinued for this indication.

chronic idiopathic urticaria.[3,87] Two randomized control trials have evaluated the efficacy of omalizumab in CRSwNP, one of which reported a small improvement in polyp size and symptoms, while the other did not show any clinical benefit.[12,13,86] Similar to the above studies on biologics in CRS, however, both are limited by sample size and a lack of long-term follow-up. Phase 3 clinical trials for the treatment of patients with CRSwNP with omalizumab are ongoing.[43]

A recent study examined the effects of omalizumab therapy in patients with CRSwNP,[19] wherein 25 patients with severe asthma and comorbid CRSwNP undergoing omalizumab therapy for their pulmonary disease were evaluated. The rates of antibiotic prescriptions for sinusitis before and after omalizumab treatment were investigated, and a significant 37% reduction in antibiotic utilization was identified. A reduction in oral steroid dependence also resulted from omalizumab therapy, as 63% of patients decreased their corticosteroid use while on omalizumab.[19] This study supports the idea that biologic therapies may have additional benefits by reducing health-care utilization. Additional studies with larger sample sizes will help determine additional indirect benefits of anti-IgE therapies.

CRS and Inflammatory Conditions With Overlapping Pathophysiology: Potential Future Biologic Targets

Multiple biologics are under evaluation or approved for use in inflammatory diseases with overlapping pathophysiology to that of CRS such as atopic dermatitis, eosinophilic asthma, chronic urticaria, and eosinophilic esophagitis.[88] As described, asthma research has

Table 3. Biologic Therapies Targeting Th1- and Th17-mediated Inflammation.

Target	Drug	Indication	References
IFN-γ^{H}	Fontolizumab	Autoimmune disorders, CD, psoriasis, RA[a]	Reinisch et al.[36]
	Emapalumab	Hemophagocytic lymphohistiocytosis[b]	Prof et al.[37]
	AMG 811	Discoid lupus erythematosus, psoriasis[a]	Werth et al.[38]
IL-1β^{I}	Canakinumab	Still's disease, CAPS, FADPF, familial Mediterranean fever, arthritis, juvenile RA, peroxisomal disorders[c]	Rondeau et al.[39]
		Behcet's syndrome, CVD, abdominal aortic aneurysm, atherosclerosis, OA, peripheral arterial occlusive disorders, pulmonary sarcoidosis, sickle cell anemia, diabetic retinopathy[b]	
		Asthma, polymyalgia rheumatic, RA, type 1 DM, type 2 DM[a]	
	Gevokizumab	Uveitis, acne, CVD, diabetic nephropathies, giant cell arteritis, labyrinthitis, myositis, OA, Schnitzler syndrome, scleritis[b]	Owyang et al.[40]
		Pyoderma gangrenosa[a]	
	LY 2189102	CVD, RA, type 2 DM[a]	Sloan-Lancaster et al.[41]
	Rilonacept	CAPS[c]	Kapur and Bonk[42]
		Anemia, cardiovascular disorders, gout, juvenile RA, OA, polymyalgia rheumatic, RA[a]	
IL-1α/IL-1β^{I}	Lutikizumab	OA[b]	Medicine UNLo[43]
IL-1R^{I}	Anakinra	RA, CAPS[c]	Fleischmann et al.[44]
		Still's disease, juvenile RA, gout[b]	
		AS, GVHD, OA, pneumococcal infections, septic shock[a]	
	Isunakinra	Allergic conjunctivitis, xerophthalmia[a]	Goldstein et al.[45]
	IP 1510	Cachexia[b]	Ma et al.[46]
	HL 2351	CAPS, RA[a]	Medicine UNLo[43]
IL-2Rα^{J}	Daclizumab	MS, renal transplant rejection[b]	Shirley[47]
		Asthma, GVHD, hematological malignancies, immune-mediated uveitis, liver transplant rejection, psoriasis, tropical spastic paraparesis, type 1 DM, UC[a]	
	Basiliximab	Renal transplant rejection, transplant rejection[b]	Kapic et al.[48]
		UC, uveitis[a]	
	Inolimomab	GVHD[b]	Socié et al.[49]
	Denileukin diftitox	Cutaneous T cell lymphoma[c]	Kaminetzky and Hymes[50]
		Malignant melanoma, peripheral T-cell lymphoma[b]	
		Alopecia, atopic dermatitis, HIV infections, inflammatory bowel diseases, MS, psoriasis, RA, transplant rejection[a]	
	ADCT-301	ALL, AML, Hodgkin's disease, non-Hodgkin's lymphoma[b]	ADCT-301[51]
IL-6^{K}	Sirukumab	Giant cell arteritis, asthma, lupus nephritis, major depressive disorder, atherosclerosis[b]	Rovin et al.[52]
		RA[a]	
	Siltuximab	Multicentric Castleman's disease[c]	Bristol-Myers Squibb[53]
		MM, paraproteinemia[b]	
		Myelodysplastic syndromes, Non-Hodgkin's lymphoma, prostate cancer, renal cell carcinoma[a]	
	Clazakizumab	Psoriatic arthritis, RA[b]	Bristol-Myers Squibb[53]
		Anemia, cachexia, fatigue, stomatitis[a]	
	Gerilimzumab	RA, autoimmune disorders[b]	Gerilimzumab[54]
	Olokizumab	RA[b]	Olokizumab[55]
	Elsilimomab	Lymphoma, MM, posttransplant lymphoproliferative disorder[a]	Fulciniti et al.[56]
	OP-R003	Hematologic malignancies, RA[a]	Fulciniti et al.[56]
	FM101	CD, MM, RA[b]	Business Wire[57]
	EBI-031	Diabetic macular edema, uveitis[b]	EBI-031[58]

(continued)

Table 3. Continued.

Target	Drug	Indication	References
IL-6R[K]	Tocilizumab	Giant lymph node hyperplasia, juvenile RA, RA[c] Drug hypersensitivity, giant cell arteritis, vasculitis, OA, systemic scleroderma, amyotrophic lateral sclerosis, dermatomyositis, polymyalgia rheumatic, polymyositis, Schnitzler syndrome, CLL[b] AS, CD, MM, pancreatic cancer, SLE[a]	Oldfield et al.[59]
	Sarilumab	RA[c] Juvenile RA, uveitis[b] AS[a]	Huizinga et al.[60]
	Vobarilizumab	RA, SLE[b]	Vobarilizumab[61]
	Sapelizumab	Neuromyelitis optica, RA[b]	Sapelizumab[62]
	Olamkicept	Inflammatory bowel diseases[b]	Olamkicept[63]
IL-17A[L]	Ixekizumab	Psoriasis[c] Psoriasis, PA, AS, spondylarthritis, bullous pemphigoid, RA[b]	Frieder et al.[64]
	Secukinumab	AS, psoriasis, PA[c] RA, alopecia areata, atopic dermatitis[b] Asthma, CD, xerophthalmia, MS, polymyalgia rheumatic, type 1 DM, uveitis[a]	Jaleel et al.[65]
	CJM-112	Acne, hidradenitis suppurativa, psoriasis, MM, solid tumours, MS[b]	Wiendl et al.[66]
	ALX-0761	Psoriasis	Torres et al.[67]
	Bimekizumab	AS, hidradenitis suppurativa, psoriasis, PA, RA, UC[b]	Glatt et al.[68]
IL-17R[L]	Brodalumab	Psoriasis, PA[c] Spondylarthritis[b] Asthma, CD, psoriasis, RA[a]	Puig[69]
IL-22[M]	Fezakinumab	Psoriasis, RA[a]	Pfizer[70]
	Rituximab	CLL, follicular lymphoma, Idiopathic thrombocytopenic purpura, lymphoproliferative disorders, microscopic polyangiitis, nephrotic syndrome, non-Hodgkin's lymphoma, RA, GPA[c] Diffuse large B cell lymphoma, mantle-cell lymphoma, pemphigus vulgaris, transplant rejection, neuromyelitis optica, glomerulonephritis, Sjogen's syndrome[b] Dermatomyositis, GVHD, immune thrombocytopenic purpura, SLE[a]	Ciccia et al.[71]; AdisInsight[72]
IL-22R[M]	ARGX-112	Autoimmune disorders, ovarian cancer, pain, renal cancer, skin disorders[b]	Yamagata et al.[73]
IL-12/IL-23[N]	Ustekinumab	CD, psoriasis, Pa[c] Spondylarthritis, UC, atopic dermatitis, SLE[b] MS, palmoplantar pustulosis, primary biliary cirrhosis, RA, sarcoidosis[a]	arGEN-X[74]
	Briakinumab	Psoriasis[b] CD, MS, RA[a]	Ding et al.[75]
IL-23[N]	Risankizumab	Psoriasis, AS, asthma, CD, PA[b]	Papp et al.[76]
	Tildrakizumab	Psoriasis, AS, PA[b] Autoimmune disorders[a]	Reich et al.[77]
	Guselkumab	Psoriasis, PA, RA[b]	Gordon et al.[78]
	Brazikumab	CD[b]	Sands et al.[79]
	Mirikizumab	CD, Psoriasis, UC[b]	ClinicalTrials.gov[80]
	BMS-938790	Inflammation[b]	AdisInsight[81]

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; AS, ankylosing spondylitis; CAPS, cryopyrin-associated periodic syndromes; CD, Crohn's disease; CLL, chronic lymphocytic leukemia; CVD, cardiovascular disease; DM, diabetes mellitus; FADPF, familial autosomal dominant periodic fever; GPA, granulomatosis with polyangiitis; GVHD, graft versus host disease; IFN, interferon; IL, interleukin; MM, multiple nyeloma; MS, multiple sclerosis; OA, osteoarthritis, PA, psoriatic arthritis; R, receptor; RA, rheumatoid arthritis; Rα, receptor alpha subunit; SLE, systemic lupus erythematosus; UC, ulcerative colitis.

[a]Discontinued for this indication.

[b]Currently under investigation for clinical use for this indication.

[c]Approved for use (see references for specific indications).

revealed the utility of biologics in CRSwNP. However, there are biologic therapies under investigation which target the inflammatory mediators identified in other CRS endotypes (ie, Th1 and Th17 pathways). Many of these agents are undergoing development and investigation for other indications (Table 2). Given the overlapping targets with CRS-associated inflammation, these biologics may provide potential options for future biologic research specific to CRS. The following section describes the inflammatory pathways associated with Th1-, Th2-, and Th17-mediated inflammation, the predominant pathways associated with CRS. The goal of this section is to highlight the pathophysiology of CRS and how it relates to potential future targets for biologic therapies. A simplified schematic illustrating the pathophysiology of CRS with respect to subtype and inflammatory endotype as well as corresponding biologic targets is depicted in Figure 1.

CRSwNP is classically associated with Th2-mediated signaling, where thymic stromal lymphopoietin (TSLP) serves as a primary initiator of inflammatory activity.[89] TSLP induces the expression of OX40 ligand (OX40L), which causes the differentiation and activation of (CD4)-positive T cells.[89] Both TSLP and OX40L have been the target of recent drug development for treating asthma, atopic dermatitis, and allergic rhinitis.[35,90] TSLP and OX40L are elevated in nasal polyp tissue and may play an important role in the pathogenesis of CRSwNP.[91] TSLP also interacts with IL-1 to stimulate the secretion of IL-5 by mast cells. The accumulation of soluble IL-5, IL-4, and IL-13 induces the production of TSLP and chemokines, such as eotaxins (C-C motif chemokine ligand [CCL] 11 and CCL24), in epithelial cells, creating a positive feedback loop of Th2-mediated inflammatory signaling.[92] The net effect of these cytokines/chemokines results in the recruitment, activation, and enhanced survival of eosinophils, which are elevated in patients with recalcitrant eosinophilic CRS.

Eosinophils have been identified as a potential target for biologic development.[93] These therapies could potentially be translated to eosinophilic CRS using a similar rationale supporting the benralizumab and dupilumab investigations in CRS. Chemokine receptors found on eosinophil membranes and their ligands involved in activation are examples of targets in severe asthma.[93] Bertilimumab (Table 2[B]) is an antibody that binds CCL11 (eotaxin-1), one of the most potent chemoattractants for eosinophil migration.[28,29] Bertilimumab has been shown to reduce eosinophilia, and clinical trials for this biologic are planned for severe asthma.[28,29] Similarly, sialic acid-binding immunoglobulin-like lectin (Siglec)-8 is a receptor found on mature eosinophils and when activated induces apoptotic cell death in eosinophils.[93] Anti-Siglec-8 antibodies are currently under preclinical investigations.[10]

CRSsNP is classically associated with the Th1 pathway, which is initiated by the release of IL-12 from dendritic cells and macrophages upon antigen exposure.[29] This promotes the differentiation of naive T cells into Th1 cells that produce IFN-γ and IL-2.[94] IFN-γ stimulates neutrophil oxidative burst, phagocytosis, and chemotaxis.[95] This pathophysiology is also seen in other inflammatory conditions such as multiple sclerosis, psoriasis, and rheumatoid arthritis.[96] The Th17 pathway is also associated with CRSsNP; dendritic cells sense pathogens and produce IL-23.[97] IL-23, in combination with IL-1β and IL-6 secreted from T cells, induces the expression of IL-22 from various cells.[97] IL-22 works synergistically with IL-17 from Th17 cell and TNF-α to produce cytokines/chemokines that induce downstream inflammatory effects, including the recruitment of neutrophils.[97]

These potent inflammatory mediators of Th1- and Th17-associated inflammation have been the focus for biologic development in other chronic inflammatory diseases. For example, IL-1, IL-1R, and IL-1α/IL-1β have been targeted for treating rheumatoid or osteoarthritis.[42,44,98] Several additional biologics are either approved or under evaluation for treating rheumatoid arthritis, including monoclonal antibodies against IL-6/IL-6R and INF-γ.[59,60,99] Anti-IL-2Rα therapies have also been examined for use in multiple sclerosis.[100] Biologic therapies targeting IL-17, IL-12/IL-23, and IL-22 are indicated for psoriasis and/or Crohn's disease.[67,69,70,76,79,101]

Each of these diseases shares a common inflammatory pathway with CRSsNP, however, whether there is any clinical relationship remains unclear.[102,103] Additional studies are necessary to investigate the potential relationship between CRS and other inflammatory conditions, which may further inform the diagnosis and treatment options for patients with CRS.

Risks of Biologic Therapies

While biologic therapies are promising for CRS, they are not risk free. The majority of research on these therapies in CRS is limited to small randomized control trials and case series with limited follow-up durations. The safety profiles for these medications have been examined more thoroughly in other diseases such as asthma and chronic idiopathic urticaria.[104] Table 1 details the side effects of the biologics currently under investigation for use in CRSwNP. The most common reactions are injection site reactions (8%–45%) and headaches (6%–19%).[104] Hypersensitivity reactions and anaphylaxis are reported to occur in less than 1% of patients, but reactions can be life-threatening.[104] More serious reactions have been reported with specific therapies. Dupilumab has been associated with herpes simplex reactivation,

conjunctivitis, and a risk of serum sickness.[104] Omalizumab is associated with a risk of cardiovascular complications, including pulmonary embolism, deep vein thrombosis, myocardial infarctions, and unstable angina.[104] Omalizumab additionally has been associated with an increased risk of malignancy; however, recent studies have shown that there is no increased rate of cancer in asthma patients on long term (9 years) of Omalizumab.[105]

There are also significant costs associated with biologic therapies, which direct costs range from $10 000 to $40 000 annually.[106,107] If biologic therapies provide patients with long-term improvements in disease control and reduce the need for revision surgeries, biologics may prove to be a cost-effective intervention. However, additional long-term studies are necessary before the cost-effectiveness and value of biologic therapies in CRS can be determined.

Conclusion

Biologics are a promising therapeutic for the personalized treatment of patients with CRS. Targeted therapies may help physicians tailor an appropriate therapy regimen with respect to inflammatory profile, such that patients receive relief with decreased risks compared to multiple revision surgeries or long-term corticosteroid use. However, our limited understanding of the underlying pathophysiology and lack of objective biologic markers of disease severity and treatment outcomes relating to QOL remains a barrier to adequately select and treat those patients in a personalized manner. Further research is needed to determine the long-term benefits and risks and safety profiles of currently available biologic therapies before they are recommended for routine use. As the pathogenesis of CRS is increasingly understood, biologics prescribed for similar inflammatory processes, such as asthma and atopic dermatitis, may serve as a starting point for future research in CRS. The majority of biologic development has been focused on eosinophilic and allergic CRS, suggesting that future development should target Th1, Th17, and noneosinophilic endotypes.

Declaration of Conflicting Interests

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